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ABSTRACT

Background: Chronic kidney disease (CKD) is estimated to affect up to 6% of women of reproductive age. Maternity care represents an opportunity for early diagnosis but there is limited understanding of CKD aetiology occurring in or revealed by pregnancy.

Methods: A retrospective evaluation of renal biopsies during and after pregnancy between 2000-2015 was undertaken. A large academic health centre pathology database was searched for free text pregnancy-related terms, restricted to typology code 71000 (kidney). Indications and findings of postpartum renal biopsies were reviewed.

Results: 63 renal biopsy reports were identified. Of 45 biopsies performed postpartum, 34 (75.6%) investigated persistent postpartum proteinuria. 20/34 (70.6%) of these biopsies yielded a primary renal disease, and 6/34 (17.6%) women had progressed to end stage renal disease at latest follow up.

Conclusion: Renal biopsy findings of women investigated for persistent postpartum proteinuria revealed a high incidence of histological diagnosis of *de novo* renal disease.

Introduction

Chronic kidney disease (CKD) stages 1 to 5 are estimated to affect up to 6% of women of reproductive age,¹ with early stage renal disease (stages 1 and 2) accounting for the majority of cases.^{1,2} Pregnancies in women with CKD are associated with higher rates of maternal and perinatal morbidity and mortality,³ even in those with mild disease, compared to low risk pregnant populations.⁴ Proteinuria may be the only indication of renal pathology before a reduction in glomerular filtration rate (GFR) and routine urine testing in pregnancy represents an opportunity for early diagnosis.⁵

Ongoing proteinuria identified postpartum can be a manifestation of resolving glomerular impairment secondary to pre-eclampsia or primary renal disease. Data from small cohort studies suggests that at six months postpartum proteinuria secondary to pre-eclampsia has resolved in over 95% of women;⁶ however women with persistent proteinuria following pre-eclampsia are reported to have high rates of underlying renal disease.⁷ Our objective was to review the indications and findings of renal biopsies performed postpartum at a large London hospital, and determine rates of diagnosis of new renal disease.

Methods

Data collection

The hospital pathology database was searched using free text terms: 'Pregnancy', 'pregnant', 'postpartum' and 'post-partum' between 2000 and 2015, with no restriction other than typology code 71000 (kidney). All histology reports were reviewed by FCR. Clinical information on indication for biopsy and maternal age was extracted from the biopsy reports,

and final histological diagnosis recorded. Biopsy slides were reviewed by FCR and PB in indeterminate cases and diagnosis assigned if there was consensus.

Further data extraction in subgroups with sufficient numbers ($n > 30$) to enable meaningful analysis of biopsy findings and follow-up was undertaken, including serum creatinine concentrations and protein: creatinine ratio (PCR) values at delivery, at the time of biopsy and at follow up (1 year post biopsy and most recent assessment) were extracted from hospital laboratory records. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The work was registered as an audit at the local hospital site and approved by the audit committee.

Renal biopsy processing

Routine stains were performed on all renal biopsy sections (Hematoxylin and Eosin, Haematoxylin/van Gieson, Congo Red, Periodic Acid Schiff and Periodic acid silver methenamine stain) and immunohistochemistry for IgM, IgG, IgA, C9, C3 and C1q undertaken prior to reporting by a specialist renal histopathologist. Electron micrographic images were reviewed where appropriate.

Results

Sixty-three renal biopsies related to pregnancy were identified, of which 55 were eligible for further evaluation in the study. Case selection is illustrated in Figure 1. The indications for all renal biopsies are shown in Table 1. 3.6% of biopsies were taken pre-pregnancy, 14.5% during pregnancy and 81.8% postpartum. Median maternal age at time of biopsy was 33 years (interquartile range (IQR) 29, 37).

Biopsies performed pre-pregnancy and during pregnancy

There were eight biopsies performed during pregnancy between 2000-2015 including two in women with known systemic lupus erythematosus (SLE), with active lupus nephritis confirmed in both. All women had proteinuria including six with nephrotic range (proteinuria > 3.5g/day) urinalysis (one with SLE). In the remaining six women a variety of diagnoses were made: diabetic glomerulopathy, minimal change disease, fibrillary glomerulopathy with extensive chronic renal damage, pre-eclampsia, late IgA nephropathy, and in one case no diagnosis was reached. Data on gestational age at biopsy were available in six cases, median gestational age at the time of biopsy was 13 weeks (IQR 12-15).

There were two biopsies performed specifically prior to pregnancy in women with renal transplants. One woman had recently switched immunosuppressive agent and was planning a pregnancy, and the other had deteriorating renal function with her third renal transplant and was planning a pregnancy. Biopsies in both cases demonstrated chronic renal allograft damage.

Biopsies performed postpartum

The majority (34/45; 75.6%) of postpartum renal biopsies were performed to investigate persistent postpartum proteinuria and further data extraction and analysis was conducted on this subgroup. These biopsies were performed a median of 24 months (IQR 9, 36) after delivery. Histological findings of biopsies investigating persistent postpartum proteinuria are shown in Table 2. Most biopsies (24/34; 70.5%) to investigate persistent postpartum proteinuria identified glomerular pathology, with hyperfiltration changes being most

common ('overload' or secondary focal segmental glomerulosclerosis (FSGS) 11/34; 32.4%). Biopsies with 'overload changes' (n=8) ([primary histological finding of glomerulomegaly](#)) were taken at a median of 12 months (IQR 9, 48) postpartum, whereas those revealing secondary FSGS (n=3) ([primary histological finding of segmental areas of scarring](#)) were performed a median of 36 months postpartum (IQR 30, 60); whilst there was no statistically significant difference in biopsy timing this was limited by small numbers in each group.

Renal function and progression to end stage renal disease in women with postpartum proteinuria

Median eGFR was 109 ml/min/1.73m² (IQR 69, 115), and median urinary PCR was 167 mg/mmol (IQR 146, 219) at time of biopsy in women investigated for persistent postpartum proteinuria. Creatinine, eGFR and PCR at time of biopsy, 1 year post biopsy and at latest follow up are shown in Table 3. There were no statistically significant differences between markers of renal function and proteinuria at time of biopsy, 1 year post biopsy and follow-up but data were absent for several women due to clinical care continuing at their local hospital, and follow up data included women who had progressed to end stage renal disease (ESRD) and were receiving renal replacement therapy or a renal transplant.

Six of 34 (17.6%) of women biopsied for persistent postpartum proteinuria had progressed to end stage renal disease (ESRD) at latest follow up. Median months between biopsy and latest follow up in these women was 160 (IQR 148, 181). Five had received a renal transplant and one woman was on dialysis. Biopsy findings included: overload changes/FSGS (n=2), primary FSGS (n=2), late chronic parenchymal damage (n=1), and hypertensive renal disease (n=1).

Median eGFR at time of biopsy in women who developed ESRD compared to those who did not was 25 ml/min/1.73m² (IQR 11, 91) and 113 ml/min/1.73m² (IQR 33, 129) respectively.

Discussion

Principal findings

Renal biopsy findings of women being investigated for persistent postpartum proteinuria revealed a high incidence of histological diagnosis of *de novo* renal disease with high rates of progression to ESRD (almost one in five women). Women who had progressed to ESRD at latest follow up had worse renal function at time of biopsy. Overload changes tended to be evident in biopsies performed sooner after delivery whereas FSGS lesions were more common in delayed biopsies which may indicate a histological transition from hyperfiltration to scarring. The number of renal biopsies conducted before, during or after pregnancy was small.

Study strengths and limitations

There are few studies reporting biopsies performed to investigate renal disease identified during or after pregnancy. This study investigating fifteen years of biopsy reports enhances our understanding of pregnancy as an opportunity to unmask CKD. Whilst renal biopsy reports represent the most severe end of the diagnostic spectrum, the relatively small number of reports identified in this study may indicate that kidney disease may not be easily recognised during pregnancy, is not always actively investigated, or is mild and does not meet criteria to recommend biopsy. It is likely that more severe disease is presented in this study i.e. those biopsied. However, the proportion of women with postpartum proteinuria who progressed to ESRD highlights the need for focussed care for this high-risk group.

The association between biopsies taken closer to pregnancy revealing 'overload' changes and later biopsies showing established FSGS scarring is suggestive that there may be a window of opportunity to minimise hyperfiltration injury. However, serial biopsies were not undertaken, nor would be clinically justified. Furthermore, clinical data including pregnancy outcomes, ongoing medication (e.g. Angiotensin converting enzyme inhibitors) and some follow-up data were not available due to transfer of care to different units and limited longitudinal assessment of glomerular filtration rate. A comprehensive prospective study to explore natural history of postpartum proteinuria secondary to hyperfiltration injury with complete follow-up data would enhance understanding of the contribution of maternal risk factors and pregnancy-related complications including pre-eclampsia and acute kidney injury to persistent and progressive renal pathology.

A limitation of this study was the retrospective study design; however the findings of this study highlight that performing a renal biopsy before, during or after pregnancy is uncommon. This approach enabled several years of data to be included which could not be easily achieved with prospective design.

Comparison to other studies

The high incidence of histological *de novo* renal diagnoses in our study is consistent with a published multicenter series of 75 women who had postpartum biopsies for renal disease identified in pregnancy. Two thirds of women (68%) had a primary renal disease, with FSGS also being the most common diagnosis.⁸ Whether cases were of secondary as opposed to primary FSGS was not specified in this study, and can be difficult to distinguish histologically.

A high rate of progression to ESRD in 7/47 cases (15%) where follow-up data were available at a median of 51.5 months (range 1-212) was also reported. Similarly, FSGS was identified in a third of women in a larger study of 173 pregnancy-related biopsies (11% antenatal, 89% up to 1 year postpartum) and 12.7% required renal replacement therapy in the follow up period (median follow up 42.8 months (IQR 17.4, 70.9)).⁹ In a retrospective study of women with glomerulopathies who had a pregnancy prior to their diagnosis, those who reported deterioration of renal function, worsening proteinuria, worsening blood pressure control and/or pre-eclampsia diagnosis during pregnancy were diagnosed with glomerulopathy sooner than women who had reported an uncomplicated pregnancy.¹⁰ Together with our findings these studies suggest that pregnancy or delivery may exacerbate or cause hyperfiltration injury, and reveals otherwise undiagnosed renal disease.

Summary, implications for clinical practice and future research

The findings of this study confirm that renal biopsy postpartum can reveal renal pathology which may pre-exist or develop during pregnancy, with a high rate of progression to ESRD in these young women. Currently NICE guidelines on management of Hypertension in pregnancy¹¹ recommend referral of women to a specialist for investigation if they have persistent dipstick proteinuria >2+ protein at 6 weeks postpartum following hypertensive disorders of pregnancy. Clinicians caring for women in pregnancy should liaise with Primary Care clinicians to ensure that women who are proteinuric in pregnancy (for example those that developed a hypertensive disorder of pregnancy or gestational proteinuria) have repeat urinalysis with quantification of proteinuria if appropriate at the six week postnatal check. Those with persistent proteinuria should be followed up and investigated, and referred to

~~Nephrology services in keeping with the NICE guidelineswomen that have persistent proteinuria postpartum have appropriate follow up and are investigated appropriately.~~

~~Currently NICE guidelines on management of Hypertension in pregnancy⁴¹ recommend referral of women to a specialist for investigation if they have persistent dipstick proteinuria ≥2+ protein at 6 weeks postpartum following hypertensive disorders of pregnancy. Larger prospective studies are required to evaluate the incidence of new CKD diagnoses following investigation of persistent postpartum proteinuria, disease course and strategies to slow progression especially in those with early features of hyperfiltration.~~

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